Are there benefits of low doses of ACE inhibitors, MRAs, diuretics and statins in the treatment of heart failure?

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Treatment of chronic heart failure (CHF) is very controversial. The issue of optimal doses of beta-blockers, ACE inhibitors, aldosterone receptor antagonists, statins in patients with CHF has not been conclusively addressed. Achieving the maximum tolerated doses of drugs, though related to reduced mortality, but is accompanied by an increase in adverse drug reactions.

The aim. To present and discuss our own clinical and scientific data concerning the role of beta-blockers and inhibitors of the renin-angiotensin aldosterone system, diuretics, statins in the treatment of CHF patients and optimization of dosage schemes.

Material and methods. The study included 88 patients with CHF of ischemic origin, with sinus rhythm, stage II AB, NYHA FC II–IV, 58 – with reduced LV EF (HFrEF) and 30 – with preserved LV EF (HFpEF). The mean age of patients was 69.18 ± 9.97 years, men 52 % (n = 46). The median follow-up of the CHF patients was 396 days, the maximum number of follow-up days was 1302. During the observation period, 14 endpoints were registered, which accounted for 15.91 % of events: 7 deaths (8.0 %), 2 strokes (2.3 %), 2 cases of acute coronary syndrome (2.3 %), 3 progressive heart failure cases (3.4 %). Kaplan–Mayer curves were drawn to assess survival rate, and the significance of difference between groups was calculated by the criteria of Gehan–Wilcoxon, Cox–Mantel and log-rank test. Risk factors were determined, and prognostic uni- and multi-variant Cox proportional hazards regression models were used. The cut-off values of quantitative risk factors were obtained by ROC analysis.

Results. The increase in the relative risk of adverse cardiovascular events in the CHF patients regardless of LV EF was associated with a daily carvedilol dose of more than 25 mg (HR = 1.05; 95 % CI 1.009–1.093; P = 0.0171); eplerenone – more than 12.5 mg (HR = 1.073; 95 % CI 1.005–1.144; P = 0.034), torasemide – more than 5 mg (HR = 1.13; 95 % CI 1.021–1.255; P = 0.019); rosuvastatin – more than 10 mg (HR = 1.107; 95 % CI 1.007–1.203; P = 0.035), and the trend in using atorvastatin at a dose of less than 10 mg (HR = 1.05; 95 % CI 0.951–1.165; P = 0.327). The use of ramipril in a daily dose of less than 2.5 mg was accompanied by a trend towards the 22 % reduced relative risk of adverse cardiovascular events (HR = 0.78; 95 % CI 0.384–1.580; P = 0.491).

Conclusions. Positive treatment outcomes in the CHF patients, regardless of the phenotype, were associated with low daily doses of ramipril (<2.5 mg), eplerenone/spironolactone (<12.5 mg), torasemide (<5.0 mg), rosuvastatin (<10.0 mg), but with high doses of atorvastatin (>10.0 mg).

Key words: chronic heart failure, ACE inhibitors, MRAs, diuretics, statins, treatment.

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Чи існують переваги низьких доз ІАПФ, АМР, діуретиків і статинів під час лікування хронічної серцевої недостатності?

В. А. Лисенко

Лікування хронічної серцевої недостатності (ХСН) дуже суперечливе. Питання про оптимальні дози бета-адреноблокаторів, інгібіторів АПФ, антагоністів рецепторів альдостерону, статинів у пацієнтів із ХСН остаточно не вирішене. Досягнення максимально переносних доз ліків хоча й пов'язане зі зниженням смертності, але супроводжується збільшенням побічних ефектів препаратів.

Мета роботи – навести й обговорити власні клінічні та наукові дані, що стосуються ролі бета-адреноблокаторів, інгібіторів ренін-ангіотензинової альдостеронової системи, діуретиків, статинів у лікуванні хворих на ХСН, а також оптимізації режимів дозування.

Матеріали та методи. У дослідження залучили 88 хворих на ХСН ішемічного ґенезу з синусовим ритмом, II А–Б стадії, II–IV ФК за NYHA: 58 осіб зі зниженою ФВ, 30 – зі збереженою ФВ лівого шлуночка. Середній вік хворих – 69,18 ± 9,97 року, 52 % чоловіків (n = 46). Медіана спостереження за хворими на ХСН становила 396 днів, максимальна кількість днів спостереження – 1302. За період спостереження зареєстрували 14 кінцевих точок, що становило 15,91 % подій: 7 (8 %) смертей, 2 (2,3 %) інсульти, 2 (2,3 %) випадки гострого коронарного синдрому, 3 (3,4 %) випадки прогредієнтної серцевої недостатності. Виживаність оцінювали шляхом побудови кривих Каплана–Маєра, вірогідність різниці між групами розрахували за критеріями Ґегана–Вілкоксона, Кокса–Мантела та log-rank test. Визначили фактори ризику та побудували уні- та мультиваріантні моделі прогнозу регресійним аналізом пропорційних ризиків Кокса. ROC-аналізом встановлено граничні значення кількісних факторів ризику.

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Результати. Збільшення відносного ризику несприятливих кардіоваскулярних подій у хворих на ХСН незалежно від ФВ лівого шлуночка асоціювалося з добовою дозою карведілолу понад 25 мг (ВР = 1,05; 95 % ДІ 1,009–1,093; p = 0,0171); еплеренону понад 12,5 мг (ВР = 1,073; 95 % ДІ 1,005–1,144; p = 0,034), торасеміду понад 5 мг (ВР = 1,13; 95 % ДІ 1,021–1,255; p = 0,019); розувастатину понад 10 мг (ВР = 1,107; 95 % ДІ 1,007–1,203; p = 0,035), тенденцією в разі застосування аторвастатину в дозі менше ніж 10 мг (ВР = 1,05; 95 % ДІ 0,951–1,165; p = 0,327). Застосування раміприлу в добовій дозі менше ніж 2,5 мг супроводжувалось тенденцією до зменшення на 22 % відносного ризику несприятливих кардіоваскулярних подій (ВР = 0,78; 95 % ДІ 0,384–1,580; p = 0,491).

Висновки. Позитивні результати лікування хворих на ХСН незалежно від фенотипу асоціювалися з низькими добовими дозами раміприлу (<2,5 мг), еплеренону/спіронолактону (<12,5 мг), торасеміду (<5 мг), розувастатину (<10 мг), але з високими дозами аторвастатину (>10 мг).

Ключові слова: хронічна серцева недостатність, інгібітори АПФ, антагоністи мінералокортикоїдних рецепторів (АМР), діуретики, статини, лікування.

Актуальні питання фармацевтичної і медичної науки та практики. 2021. Т. 14, № 2(36). С. 226–231

Существуют ли преимущества низких доз иАПФ, АМР, диуретиков и статинов при лечении хронической сердечной недостаточности?

В. А. Лысенко

Лечение хронической сердечной недостаточности (ХСН) очень противоречиво. Вопрос об оптимальных дозах бета-адреноблокаторов, ингибиторов АПФ, антагонистов рецепторов альдостерона, статинов у пациентов с ХСН окончательно не решен. Достижение максимально переносимых доз лекарств хотя и связано со снижением смертности, но сопровождается увеличением побочных эффектов препаратов.

Цель работы – представить и обсудить собственные клинические и научные данные, касающиеся роли бета-адреноблокаторов, ингибиторов ренин-ангиотензиновой альдостероновой системы, диуретиков, статинов в лечении больных ХСН, а также оптимизации режимов дозирования.

Материалы и методы. В исследование включили 88 больных ХСН ишемического генеза с синусовым ритмом, II А–Б стадии, II–IV ФК по NYHA: 58 человек со сниженной ФВ, 30 – с сохраненной ФВ левого желудочка. Средний возраст больных – 69,18 ± 9,97 года, 52 % мужчин (n = 46). Медиана наблюдения за больными с ХСН составила 396 дней, максимальное количество дней наблюдения – 1302. За период наблюдения зарегистрировали 14 конечных точек, что составило 15,91 % событий: 7 (8 %) смертей, 2 (2,3 %) инсульта, 2 (2,3 %) случая острого коронарного синдрома, 3 (3,4 %) случая прогредиентной сердечной недостаточности.

Выживаемость оценивали путем построения кривых Каплана–Майера, а вероятность разницы между группами рассчитана по критериям Гехана–Вилкоксона, Кокса–Мантела и log-rank test. Определены факторы риска и построены уни- и мультивариантные модели прогноза регрессионным анализом пропорциональных рисков Кокса. ROC-анализом установлены предельные значения количественных факторов риска.

Результаты. Увеличение относительного риска неблагоприятных кардиоваскулярных событий у больных ХСН независимо от ФВ левого желудочка ассоциировалось с суточной дозой карведилола более 25 мг (ОР = 1,05; 95 % ДИ 1,009–1,093; p = 0,0171); эплеренона более 12,5 мг (ОР = 1,073; 95 % ДИ 1,005–1,144; p = 0,034), торасемида более 5 мг (ОР = 1,13; 95 % ДИ 1,021–1,255; p = 0,019) розувастатина более 10 мг (ОР = 1,107; 95 % ДИ 1,007–1,203; p = 0,035) и тенденцией при применении аторвастатина в дозе менее 10 мг (ОР = 1,05; 95 % ДИ 0,951–1,165; p = 0,327). Применение рамиприла в дозе менее 2,5 мг сопровождалось тенденцией к уменьшению на 22 % относительного риска неблагоприятных кардиоваскулярных событий (ОР = 0,78; 95 % ДИ 0,384–1,580; p = 0,491).

Выводы. Положительные результаты лечения больных с ХСН независимо от фенотипа ассоциировались с низкими суточными дозами рамиприла (<2,5 мг), эплеренона/спиронолактона (<12,5 мг), торасемида (<5 мг), розувастатина (<10 мг), но высокими дозами аторвастатина (>10 мг).

Ключевые слова: хроническая сердечная недостаточность, ингибиторы АПФ, антагонисты минералокортикоидных рецепторов (АМР), диуретики, статины, лечение.

Актуальные вопросы фармацевтической и медицинской науки и практики. 2021. Т. 14, № 2(36). С. 226–231

Chronic heart failure (CHF), a major cardiovascular disorder, remains a grievous clinical condition regardless of advances in medical care [1].

CHF is associated with impaired functional capacity, as well as significant morbidity due to frequent hospitalizations. Unfortunately, despite its poor prognosis, the management of CHF is very controversial and no therapy has been so far shown to reduce mortality, especially in heart failure with preserved ejection fraction (HFpEF) [2]. The aim of personalized medicine is to offer a tailored approach to each patient in order to provide the most effective therapy, while reducing risks and adverse effects, and avoiding unnecessary treatments [3].

The issue of optimal doses of beta-blockers, ACE inhibitors, aldosterone receptor antagonists, statins in CHF patients has not been finally resolved. Achieving the maximum tolerated doses of drugs, though related to reduced mortality, but is accompanied by an increase in adverse drug reactions.

Aim

To present and discuss our own clinical and scientific data concerning the role of beta-blockers and inhibitors of the renin-angiotensin aldosterone system, diuretics, statins in the treatment of patients with HFrEF and HFpEF and optimization of dosage schemes.

Materials and methods

The study was conducted on the clinical base of the Department of Propaedeutics of Internal Medicine, Radiation Diagnostics and Radiation Therapy (Zaporizhzhia State Medical University) in the Cardiology Department of City Hospital No. 6 (Zaporizhzhia), in accordance with the Good Clinical Practice guidelines and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee of Zaporizhzhia State Medical University.

After obtaining written informed consents, the study included 88 patients with CHF of ischemic origin, stage II AB, New York Heart Association (NYHA) II–IV functional class (FC), 58 – with HFrEF and 30 – with HFpEF. The mean age of patients was 69.18 ± 9.97 years, men 52 % (n = 46). Groups of patients with different left ventricular ejection fraction (LV EF) were matched in age (P = 0.021), height (P = 0.222), weight (P = 0.835), body surface area (P = 0.587). CHF of ischemic origin was diagnosed in accordance with the Recommendations for the diagnosis and treatment of CHF (2017) of the Association of Cardiologists of Ukraine and the Ukrainian Association of Heart Failure [4].

The CHF patients with HFrEF and HFpEF did not differ in the frequency of prescribing basic drugs for the treatment of heart failure (*Table 1*).

Mean therapeutic doses of drugs used to treat the CHF patients are given in *Table 2*.

Groups of the CHF patients with different LV EF did not differ in the mean daily doses of beta-blockers, ACE inhibitors, ARBs, antiplatelet agents, statins (*Table 3*).

Groups of patients with CHF and different EF differed significantly in daily doses of torasemide (P = 0.014) and spironolactone (P = 0.028).

Cumulative endpoints were considered death, myocardial infarction, stroke, progressive heart failure, and progressive angina.

During the follow-up period (median 396 days [53–1302]), 14 endpoints were registered, which accounted for 15.91 % of events: deaths 7 cases (8%), strokes 2 cases (2.3 %), myocardial infarction 1 case (1.15 %), progressive angina 1 case (1.15 %), progressive heart failure 3 cases (3.4 %). Endpoint frequency analysis depending on the CHF phenotype did not reveal a significant difference between the study groups, 18.97 % (11/58) vs. 10 % (3/30); log-rank test (P = 0.378).

Since there were no statistical differences in the number of cumulative endpoints between the groups of CHF patients with reduced and preserved LV EF, in order to determine the effects of therapy on adverse events in this cohort of patients, a single database was created combining all the CHF patients regardless of LV EF (n = 88).

Table 1. Frequency of prescribing basic and additional drugs to the CHF patients

Group of drugs	HFrEF, n = 58	HFpEF, n = 30	P
beta-blockers	98 % (n = 57)	97 % (n = 29)	0.7694
ACEi/ARB	93 % (n = 54)	97 % (n = 29)	0.4427
– ramipril	39 % (n = 54)	23 % (n = 54)	0.1355
MRAs	100 %	100 %	1.0000
– eplerenone	67 % (n = 39)	53 % (n = 16)	0.2026
– spironolactone	33 % (n = 19)	47 % (n = 14)	0.2026
Loop diuretics	95 % (n = 55)	77 % (n = 23)	0.0127
– torasemide	84 % (n = 49)	77 % (n = 23)	0.4239
– furosemide	11 % (n = 6)	0 % (n = 0)	0.0766
Thiazide-like diuretics	15 % (n = 9)	23 % (n = 7)	0.3542
Statins	97 % (n = 56)	97 % (n = 29)	1.0000
– atorvastatin	62 % (n = 36)	67 % (n = 20)	0.6450
– rosuvastatin	34 % (n = 20)	30 % (n = 9)	0.7054
Antiplatelet agents	100 %	100 %	1.0000
– aspirin	47 % (n = 27)	40 % (n = 12)	0.5923
– clopidogrel	53 % (n = 31)	60 % (n = 18)	0.5329

Table 2. The mean therapeutic doses of drugs used to treat the CHF patients (n = 88)

Class of drugs	Name of drugs	Mean dose, M ± SD
Beta-blockers	Bisoprolol	4.18 ± 1.71
	Carvedilol	15.17 ± 11.09
ACEi	Ramipril	2.70 ± 1.99
	Enalapril	8.125 ± 6.22
	Perindopril	5.09 ± 2.42
ARB	Valsartan	184.00 ± 75.89
	Candesartan	12.00 ± 4.61
Loop diuretics	Torasemide	8.40 ± 4.50
MRA	Eplerenone	24.77 ± 9.46
	Spironolactone	21.02 ± 8.24
Antiplatelet agents	Clopidogrel	75.02 ± 0.14
	Aspirin	78.21 ± 8.46
Statins	Atorvastatin	20.89 ± 5.80
	Rosuvastatin	14.23 ± 8.57

Statistical processing of the material was performed using the software package Statistica 13.0 (StatSoft, USA), license number JPZ8041382130ARCN10-J. The Shapiro–Wilk test was used to test the normality of the quantitative data. The parameters with normal distribution were presented as the arithmetic mean and standard deviation (M ± SD). The results without normal distribution were demonstrated by descriptive statistics as median, lower and upper quartiles –

Table 3. Mean daily doses of drugs used in the treatment of CHF patients with reduced and preserved LV EF

Drug	Mean daily doses of drugs in patients with HFrEF, M ± SD	Mean daily doses of drugs in patients with HFpEF, M ± SD	P
Eplerenone	25.64 ± 9.48	22.65 ± 9.37	0.292
Spironolactone	23.68 ± 8.22	17.41 ± 7.01	0.028
Carvedilol	16.41 ± 12.26	11.46 ± 5.22	0.183
Bisoprolol	4.53 ± 1.88	3.75 ± 1.44	0.228
Ramipril	2.72 ± 2.12	2.68 ± 1.68	0.965
Enalapril	8.67 ± 7.08	6.67 ± 2.89	0.661
Perindopril	6.67 ± 2.31	4.50 ± 2.33	0.202
Valsartan	200.00 ± 80.00	173.33 ± 78.66	0.615
Candesartan	10.66 ± 4.61	16.00 ± 0.00	0.422
Atorvastatin	21.67 ± 6.96	19.50 ± 2.24	0.183
Rosuvastatin	15.88 ± 9.88	11.11 ± 4.17	0.181
Clopidogrel	75.00 ± 0.00	75.00 ± 0.00	1.00
Aspirin	76.85 ± 6.67	81.25 ± 11.31	0.136
Torasemide	9.29 ± 5.00	6.52 ± 2.35	0.014

Me (Q_{25}; Q_{75}). The quantitative variables normally and non-normally distributed in the groups were compared by T-test or Mann–Whitney test, respectively, after ascertaining the normality of distribution. Using Cox proportional hazards regression analysis, univariate and multivariate prognostic models were constructed. The ROC analysis was performed to find out the cut-off values of the parameters. The survival function was estimated via the Kaplan–Meier multiple estimation method. Gehan's Wilcoxon Test, Cox–Mantel Test, Log-rank-test were used to compare cumulative endpoints in the groups. The difference was considered statistically significant at a P-value < 0.05. All the tests were two-tailed.

Results

The study analyzed the effect of main drug classes and their daily doses on the cumulative endpoints.

The choice of beta-blocker (bisoprolol or carvedilol) did not affect long-term treatment outcomes (Log-Rank Test, P = 0.234). In addition, no dependence was found in using different doses of bisoprolol. At the same time, carvedilol in a daily dose of more than 25 mg was associated with an increased relative risk of adverse cardiovascular events (HR = 1.05; 95 % CI 1.009–1.093; P = 0.0171) in the CHF patients, regardless of LV EF.

The relative risk of adverse cardiovascular events demonstrated a decreasing trend by 22 % (HR = 0.78; 95 % CI 0.384–1.580; P = 0.491) associated with low daily doses of ramipril (less than 2.5 mg).

A comparison of mineralocorticoid receptor antagonists (MRAs) effect on the cumulative endpoints showed no statistically significant difference between use of spironolactone and eplerenone (Log-Rank Test WW = 0.03843; Sum = 12.726; Var = 3.0170; Test statistic = 0.0221269; P = 0.98235). However, the eplerenone administration in doses of more than 12.5 mg unlike spironolactone in doses of more than 12.5 mg (P = 0.800) was associated with increased risk of possible adverse cardio-vascular events (HR = 1.073; 95 % CI 1.005–1.144; P = 0.034).

Similar data were obtained analyzing the effect of loop diuretic torasemide on the cumulative endpoints. Torasemide in a daily dose of more than 5 mg significantly increased the relative risk of adverse events (HR = 1.13; 95 % CI 1.021–1.255; P = 0.019).

As for the other classes of drugs effect on the cumulative endpoints in the CHF patients, the dependence of the results on the daily dose of statins is noteworthy. The use of rosuvastatin in a daily dose of more than 10 mg was associated with an increase in the relative risk of cardiovascular events by 10 % (HR = 1.101; 95 % CI 1.007–1.203; P = 0.034). Despite the lack of a significant difference between the effect of rosuvastatin and atorvastatin on the cumulative endpoints in the CHF patients (Log-Rank Test WW = -0.3304; Sum = 12.627; Var = 2.7681; Test statistic = -0.198585; P = 0.84259), such an association was not confirmed when using atorvastatin (Log-Rank Test, p = 0.435). In addition, the ROC analysis showed a reverse trend towards increased relative risk of adverse cardiovascular events in the CHF patients taking atorvastatin in doses less than 10 mg per day.

Discussion

Beta-blockers and drugs that affect the renin-angiotensin-aldosterone system (ACE inhibitors / ARBs) have proven to be highly effective in the treatment of patients with CHF in numerous randomized controlled trials, and their combination remains a cornerstone of basic therapy. We did not find any difference in the effect of bisoprolol and carvedilol on the endpoints among the CHF patients in our study. However, it should be noted that an increase in the number of adverse events with increasing dose of carvedilol was observed. In our opinion, this association of an increased risk of adverse cardiovascular events with daily doses of carvedilol over 25 mg was due to the need to prescribe higher doses for the CHF patients with more severe disease.

An interesting result of our study was a 22 % reduction in the relative risk of adverse cardiovascular events in the CHF patients associated with low daily doses of ramipril (less than 2.5 mg). In real clinical practice, 80 % of CHF patients receive doses of ACE inhibitors lower than the recommended.

Studies [5] have proven an absence of significant difference between the effects of low and high doses of ACE inhibitors on mortality (HR = 0.95; 95 % CI 0.87–1.02; P = 0.15), rehospitalization for decompensated HF (HR = 0.94; 95 % CI 0.70–1.26; P = 0.68), as well as 2 times less incidence of hyperkalemia at low doses (Odds ratio = 2.07; 95 % CI, 1.20–3.59; P = 0.01).

In respect of diuretics, loop diuretics were prescribed significantly less often (77 % vs. 95 %; P = 0.0127) in the patients with HFpEF in our study, which is fully compatible with international and Ukrainian recommendations for the treatment of CHF patients. Groups of CHF patients with different EF also differed significantly in daily doses of torasemide (P = 0.014) and spironolactone (P = 0.028). It is obvious that patients with HFrEF required higher doses of these diuretics due to more pronounced fluid retention in the body.

The study on different doses of torasemide effect on cumulative endpoints allowed us to find that higher doses of the drug were associated with an increased relative risk of adverse cardiovascular events in the CHF patients. It is worth mentioning that this effect was not associated with the drug, but with the need to prescribe higher doses of torasemide in the CHF patients with a more severe course, i.e. with severe fluid retention.

Concerning spironolactone, our study showed the upward trend of risks similar to torasemide, but it did not reach the level of statistical significance (HR = 1.02; 95 % CI 0.894–1.157; P = 0.800). The increased risk of adverse events was observed at doses of spironolactone more than 12.5 mg (the area under the ROC curve 0.556; P = 0.725), but not significant.

No statistically significant difference between the groups of patients who used spironolactone or eplerenone (Log-Rank Test, WW = 0.03843, Sum = 12.726, Var = 3.0170, Test statistic = 0.0221269, P = 0.98235) was revealed by comparing the effect of mineralocorticoid receptor antagonists on cumulative endpoints. However, only the eplerenone use at doses more than 12.5 mg per day in contrast to spironolactone at the same doses, was associated with the significantly increased risk of adverse cardiovascular events by 7 % (P = 0.034).

The positive effect of MRAs in cardiac pathology has been proven in studies RALES [6], TOPCAT [7]. It has been shown that even low doses of MRAs provide a protective effect. The use of high doses of MRAs increased the risk of hyperkalemia. In the EMPHASIS HF study, the incidence of hyperkalemia (K+ >5.5 mmol/L) was 11.8 % in the eplerenone group and 7.2 % in the placebo group (P < 0.001). Importantly, a significant difference in the incidence of hyperkalemia in patients receiving eplerenone or placebo did not lead to an increase in mortality. A post hoc analysis of the EPHESUS study also showed that in patients with congestive heart failure, a 4.4 % increase in the incidence of hyperkalemia in the eplerenone group was not accompanied by an increase in a mortality or hospitalization rate [8]. Similar results were obtained in the RALES study with spironolactone treatment [6].

A multicenter, prospective, randomized, double-blind, placebo-controlled study of Aldo-DHF examined the effect of spironolactone at a daily dose of 25 mg compared with placebo on the diastolic function and physical well-being of 422 patients with HFpEF. The observation period for patients was 12 months. Spironolactone improved diastolic function and caused reverse LV remodeling, but did not affect maximal exercise, patient symptoms, or the quality of life [9].

In a randomized double-blind trial TOPCAT, which included 3445 individuals, patients with symptomatic heart failure and EF ≥45 % were randomized to receive spironolactone 15–45 mg per day or placebo. The mean follow-up was 3.3 years. In this study, spironolactone did not significantly reduce morbidity, the primary cumulative point – death from cardiovascular causes, cardiac arrest or hospitalization rate due to progression of heart failure [7].

In a large meta-analysis of 16.321 patients from 15 randomized controlled trials, MRA therapy reduced the risk of cardiovascular death, all-cause mortality, and cardiac hospitalization rate in patients with HFrEF, but these benefits were not demonstrated in patients with HFpEF [2].

In a meta-analysis of 14 randomized controlled clinical trials involving 6 428 patients with HFpEF or myocardial infarction with preserved EF, MRA therapy reduced the number of hospitalizations for CHF by 17 %, improved diastolic function, and resulted in improved remodeling and life. However, MRA therapy had not been able to reduce all-cause mortality [10].

Statins are usually prescribed to patients with CHF of ischemic origin to prevent cardiovascular complications. Analysis of the statin effect on the endpoints in our study suggests that these drugs have dose-dependent properties. So, the clinical efficacy of atorvastatin in the CHF patients increased with increasing dose, while the best long-term results were observed when using rosuvastatin in a daily dose of less than 10 mg. Similar results were obtained in the study PROVE-IT TIMI [11]: high doses of atorvastatin to a greater extent than high doses of pravastatin reduced the risk of developing CHF in patients with acute coronary syndrome (HR= 0.55; 95 % CI, 0.35–0.85, P = 0.008). However, these data relate to the primary prevention of CHF in patients with acute coronary syndrome.

The influence of molecular differences of statins on their pharmacological and pleiotropic effects is probably important. The cardiac effects of atorvastatin may be related to its lipophilic properties and ability to penetrate cardiomyocytes as opposed to hydrophilic rosuvastatin. However, in the PEARL study [12] with lipophilic pitavastatin in CHF patients, there were no differences in the frequency of the primary endpoint (hospitalization due to worsening of heart failure and cardiac death) compared with a placebo group. In this study, a subgroup of patients with EF ≥30 showed a slightly lower incidence of primary endpoint on pitavastatin treatment compared with placebo, whereas patients with EF <30 % taking this drug, in contrast, demonstrated a tendency to reach it more frequently.

The non-lipid effects of rosuvastatin have the potential to promote endogenous tissue regeneration and improve LV EF in CHF. Rosuvastatin has been shown to activate circulating progenitor cells in CHF, which promotes neovascularization and enhances endothelial function. Correction of vascular abnormalities partially led to an increase in LV function by +27 % (P < 0.001, compared with placebo) [13].

Despite the positive preconditions for the rosuvastatin action in heart failure patients in the UNIVERSE study, negative results were obtained with the use of rosuvastatin in CHF. The authors believe that the expected beneficial effect of 26 weeks of statin therapy on cardiac remodeling may have been offset by an increase in collagen metabolism markers (Serum types I and III N-terminal procollagen peptide (PINP and PIIINP), and a decrease in plasma CoQ10 levels in CHF patients [14]. However, treatment with any statin, not just rosuvastatin, reduces circulating CoQ10. This effect of statins is not associated with drug solubility, intensity or duration of treatment [15].

Conclusions

Positive treatment outcomes (according to the Cox proportional-hazards regression analysis) in the CHF patients, regardless of the phenotype, were associated with low daily doses of ramipril (<2.5 mg), eplerenone/spironolactone (<12.5 mg), torasemide (<5 mg), rosuvastatin (<10 mg), but with high doses of atorvastatin (>10 mg).

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